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EXAMINER	
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ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/507,385	YOSHIMURA, TEIZO	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-13,18-33 and 46-57* is/are pending in the application.

4a) Of the above claim(s) *26-33 and 46-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-13,18-25,55-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission filed on 11-10-2009 has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 11-13, 18-33 and 46-60 are currently pending. Claims 11-13, 18-20, 23, 55 and 57-59 have been amended, claims 1-9 and 15-17 have been cancelled and claim 60 has been added by Applicant's amendment filed on 11-10-2009. Claims 26-33 and 46-54 were previously withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 23-25 were previously rejoined with claims 11-22 in the office action filed on 11-14-2008.

Note that the claims are examined to the extent that they read on the elected species: granulocyte-macrophage-colony stimulating factor as the DDR1-activating agent inducing expression of DDR1 and a CD-40 ligand as the additional agent that enhances macrophages or dendritic cell maturation. Note that because the genus claim is not allowable as originally claimed, no other species will be rejoined for search and examination.

Therefore, claims 11-13, 18-25 and 55-60 are currently under examination to which the following grounds of rejection are applicable.

Response to arguments

Withdrawn objections/rejections in response to Applicants' arguments or amendments

Claim Rejections - 35 USC § 103

In view of Applicants' amendment, rejection of claims 11-13, 18-25, 55, and 57-59 under 35 U.S.C. 103(a) as being unpatentable over Radziejewski et al., (US Patent 6,022,694, Date of Patent Feb 8, 2000), in view of Lipford et al., (US Pub No. 2003/0148316, Date of Publication August 7, 2003) has been withdrawn.

Though the DDR1 is one of the markers expressed in dendritic cells disclosed by Lipford et al., in US provisional application No. 60/309,260, filed on Aug. 1, 2001, DDR1 was not upregulated nor modulated by CpG oligonucleotides. Accordingly, the combination of Radziejewski et al., and Lipford et al., does not suggest or teach that contacting the immature dendritic cell with an effective amount of a DDR1-activating antibody that specifically binds DDR1, induces maturation of dendritic cells.

In view of the withdrawn rejection, applicant's arguments are rendered moot.

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In view of Applicants' amendment, rejection claim 56 under 35 U.S.C. 103(a) as being unpatentable over Radziejewski et al., (US Patent 6,022,694, Date of Patent Feb 8, 2000), in view of Lipford et al., (US Pub No. 2003/0148316, Date of Publication August 7, 2003) a applied to claims 11-25, 55, and 57 above, and further in view of Vogel et al., (WO 98/34954; Date of Patent 13 August 1998) has been withdrawn.

In view of the withdrawn rejection, applicant's arguments are rendered moot.

Rejections maintained

Claim Rejections - 35 USC § 112- First paragraph- New Matter

Claims 12, 13 and 57 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Response to Applicants' remarks as they apply to rejection of claims 12, 13 and 57 under 35 U.S.C. 112, first paragraph

At page 11 of the remarks filed on 10-19-2009, Applicants essentially argue that: **1)** "monocytes are, in fact, immature macrophages and immature dendritic cells (Specification, page 13, lines 8-16; page 19, lines 28-29; page 74, lines 8-24), **2)** "the specification clearly discloses that DDR1 mRNA (see page 47, lines 1-8) and protein (see page 49, lines 9-23) levels are up-regulated in immature macrophages or immature dendritic cells derived from PBMC when the cells are incubated in the presence of GM-CSF, tumor necrosis factor-a, interleukin-1~3, lippolysaccharide, phytohemagglutinin, or fetal calf serum, and that up- regulation of DDR1 is detected on the surface of the cells by an antibody that recognizes DDR1 (see page 82, lines 5-9)", and **3)** "The specification clearly describes a nexus between the activation of DDR1 with a DDRl-activating antibody and the up-regulation of cytokines and chemokines secreted into the cell medium". The above arguments have been fully considered but deemed unpersuasive.

Regarding 1), the fact that the as-filed specification teaches at page 13, lines 9-13, that "a dendritic cell precursor is a DC1 cell that differentiates into a myeloid dendritic cell or a

monocyte that differentiates into a macrophage which, in turn, differentiates into a dendritic cell" is not disputed.

Additionally, the specification teaches at page 12, lines 1-7, that:

> "Immature dendritic cells originate in the bone marrow and reside in the periphery as immature cells. In one embodiment, a dendritic cell is a myleoid dendritic cell. Myeloid dendritic cells (e.g. monocytes) differentiate from dendritic cell precursors called "DC1" while plasmacytoid dendritic cells differentiate from dendritic cell precursors termed "DC2".

Moreover, the specification unmistakably teaches that:

> "the ability of DCs to regulate immunity is dependent on DC maturation. A variety of factors can induce differentiation following antigen uptake and processing within DCs, including: contact with whole bacteria or bacterial-derived antigens (e.g. lipopolysaccharide, LPS), cytokines (e.g. TNF-α, IL-4, GM-CSF), ligation of select cell surface receptors (e.g. CD40) and viral products (e.g. double-stranded RNA). During their conversion from immature to mature cells, DCs undergo a number of phenotypical and functional changes.

Thus the Examiner agrees with Applicants that myleoid dendritic cells, or a monocyte, and plasmacytoid dendritic cells are dendritic cell precursors that do not express DDR1 or express low levels of DDR1, and that dendritic cell precursors differentiate into mature dendritic cells expressing high levels of DDR1 (page 13, lines 14-19). Moreover, the examiner agrees with Applicants that a macrophage is "a large white blood cell derived from monocytes (a subclass of mononuclear leukocytes)" (page 19, lines 3-5).

Regarding 2), with respect to applicants' argument that, " DDR1 mRNA (see page 47, lines 1-8) and protein (see page 49, lines 9-23) levels are up-regulated in immature macrophages or immature dendritic cells derived from PBMC when the cells are incubated in the presence of GM-CSF, tumor necrosis factor-α, interleukin-1β, lippolysaccharide, phytohemagglutinin, or

fetal calf serum" is not found persuasive because it is noted that the features upon which applicant relies (i.e., up-regulated in immature macrophages or immature dendritic cells derived from PBMC when the cells are incubated in the presence of GM-CSF, tumor necrosis factor-a, interleukin-1β, lippolysaccharide, phytohemagglutinin, or fetal calf serum according to the instant specification, for example, at page 19, lines 21-25) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). This is the case here. The claims do not recite that a variety of factors can induce differentiation following antigen uptake and processing within DCs, including: GM-CSF, a factor which modulates the maturation and function of dendritic cells (page 15, lines 13-15). Hence the argument is not persuasive as they argue limitations that are not present in the claims.

Regarding 3), with respect to applicants' argument that, " between the activation of DDR1 with a DDRl-activating antibody and the up-regulation of cytokines and chemokines secreted into the cell medium " is not found persuasive because it is noted that the features upon which applicant relies (i.e., up-regulation of cytokines and chemokines secreted into the cell medium) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Hence the argument is not persuasive as they argue limitations that are not present in the claims.

New Grounds of Rejection

Claim Rejections - 35 USC § 112-First paragraph-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-13, 18-25 and 55-60 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

A method for enhancing maturation of an immature macrophage or an immature dendritic cell that expresses discoidin domain receptor 1 (DDR1), comprising, contacting the immature macrophage or the immature dendritic with an affective amount of a DDR1-activating antibody that specifically binds DDR1 in the presence of differentiation agents that comprise granulocyte-macrophage-colony stimulating factor (GM-CSF), IL-4, and tumor necrosis factor-α (TNF-α) wherein the DDR1-activating antibody enhances GM-CSF, IL-4 and TNF-α -mediated maturation of an immature macrophage or an immature dendritic cell,

does not reasonably provide enablement for a method of inducing maturation of an immature macrophage or an immature dendritic cell that expresses a DDR1 merely by contacting the immature macrophage or the immature dendritic cell with DDR1-activating antibody that specifically binds DDR1 thereby inducing maturation of the immature macrophage or the immature dendritic cell.

The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with this claim. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims, when given the broadest possible interpretation, encompass a method for inducing maturation of immature dendritic cells (iDCs) that express DDR1 by solely contacting said immature dendritic cells with an affective amount of a DDR1-activating antibody that specifically binds DDR1 so as to induce maturation of immature dendritic cells. Claim 12 further limits claim 11 to contacting the immature dendritic cells that express DDR1 with GM-CSF which upregulates the expression of DDR1, claim 13 further limits claim 11 to contacting the immature dendritic cells that express DDR1 with an agent that upregulates DDR1 expression from the group consisting of tumor necrosis factor-α, interleukin-1β, lipopolysaccharide, phytohemagglutinin, fetal calf serum or a combination thereof and claim 19 further limits claim 11 to contacting the immature dendritic cells that express DDR1 with a differentiation agent which is CD40. The specification provides insufficient data to enable claims directed to the method as broadly claimed. Thereby, specific issues including contact of iDCs with several cytokines such as GM-CSF, IL-4, TNF-α, or other activators required for maturation of immature dendritic cells to mature dendritic cells (e.g., able to stimulate resting naive T cells in primary immune responses) have to be examined and considered for patentability regarding the broadly claimed methods.

Insofar as maturation of iDCs, the specification discloses at page 76, lines 1-10 that monocytes were incubated in the presence of IL-4 and GM-CSF for 5 days to produce iDCs, and then for an additional 2 days in the presence of IL-4, GM-CSF, and TNF-α to produce mature

DCs (mDCs). Moreover, the specification discloses that DDR1a is the dominant isoform in an early stage of DC maturation, whereas DDR1b becomes the dominant isoform in mDCs (page 76, lines 28-30). Furthermore, to determine the role of DDR1 in DC maturation, monocytes where incubated with IL-4 and GM-CSF to obtain iDC. For maturation, iDCs were incubated with TNF-α (50 ng/ml). For activation of DDR1 on DCs, the cells were incubated in the presence of either agonistic anti-DDR1 IgM (513) or control IgM, and the expression of CD80, CD83, CD86, and HLA-DR was measured using a flow cytometer (page 76; lines 1-9). Additionally, the specification illustrates in FIG. 9, that immature (iDCs) showed only a weak activity to activate allogeneic MLR and activation of DDR1 solely with the 513 antibody had no effect. TNF-α or LPS-induced mDCs markedly activated allogeneic MLR in a cell number-dependent manner. The specification concludes that activation of DDR1 promotes functional maturation of DCs in combination with other DC maturation-inducing agents (page 77, lines 18-20). However, the as-filed application is silent about any factual data disclosing a method of maturation of iDC merely by contacting iDC with agonistic anti-DDR1 IgM (513) without the presence of other cytokines.

In relation to maturation of immature macrophages, the specification discloses that monocytes migrate into tissues and differentiate into macrophages. Moreover, monocytes express low levels of DDR1. In another embodiment, monocytes do not express DDR1 (FIG. 1)(page 19, lines 28-30). Furthermore, the specification discloses that purified monocytes were allowed to adhere and adherent cells were induced to differentiate into macrophages by incubation in the presence of GM-CSF (50 ng/ml) for 5 to 7 days to produce GM-CSF-induced macrophages (GM-macrophages). Five-day GM-macrophages were incubated for additional 2

days with GM-CSF in the presence of an agonistic anti-human DDR1 monoclonal mouse against the extracellular domain of DDR1 (IgM 513) resulting in autophosphorylation of DDR1 (DDR1a+DDR1b) in response to agonistic antibody, but not to control antibody (page 64, lines 8-30). No other specific teachings are provided of any other representative number of methods for maturation of immature macrophages by merely contacting immature macrophages with agonistic anti-DDR1 IgM (513) without the presence of other cytokines. The detail of the disclosure provided by the Applicant, in view of the prior Art, must encompass a wide area of knowledge to enable one of ordinary skill in the art at the time of the invention to practice the invention without undue experimentation. However, as it will be discussed below this undue experimentation has not been overcame by the as-filed application. Though the specification defines as inducers of iDCs maturation: TNF-α, LPS, PMA and GM-CSF (page 19, lines 20-25), the broad aspects of inducing maturation of an immature macrophage or an immature dendritic cell that expresses DDR1 by merely contacting the immature macrophage or the immature dendritic cell with a DDR1-activating antibody that specifically binds DDR1 is commensurate with the disclosure of the as filed specification.

In relation of maturation of dendritic cells from PBMC, Lipford et al.,(U.S. Patent Publication 2003/0148316) discloses that maturation of dendritic cells from PBMC by treatment with GM-CSF and IL-4 . Optionally, maturation of DCs to professional APCs can be initiated by T cells expressing CD40 ligand (CD40L) or directly via engagement of pathogen constituents displaying conserved molecular patterns, also termed pathogen-associated molecular patterns (PAMP) (page 1, paragraphs [0003]-[0004]). Moreover, Lipford et al., teaches that maturing DCs express T cell-costimulating molecules on their surface, such as CD80, CD86, and CD40,

and release soluble mediators, such as cytokines and chemokines. Likewise, Brand et al., (*Eur J Immunol.* 1998, pp. 1673-80, of record) discloses that maturation of precursor monocytes into macrophages and dendritic cells by addition of cytokines including GM-CSF/ IL-4, TNF-α, and others (p. 1673, col. 2; p. 1677, col. 2). Thus cytokines such as GM-CSF/ IL-4, TNF-α are used to produce dendritic cells *in vitro*. .The claimed invention as a whole is not adequately described in the specification and is not conventional in the art as of applicants' effective filing date.

As set forth above by the nature of the invention, the state of the prior art, neither the prior art of record nor the as-filed specification provides sufficient guidance to enable a person skilled in the art to promote maturation of immature dendritic cells by the claimed method other than by using a DDR1-activating antibody that specifically binds DDR1 in the presence of appropriate cytokines including GM-CSF, IL-4, and TNF-α. Even if in iDCs expressing DDR1 were contacted *in vitro* with agonistic anti-DDR1 IgM (513), there is no evidence in the prior art or the specification that these iDCs can mature merely by activation of DDR1 signal without activation of other receptors during the process of maturation, clearly indicating that DDR1 acts as a costimulating receptor for DC maturation. Accordingly, the issue of claiming broadly a genus of methods to induce maturation of an iDC or an immature macrophage by merely contacting an iDC with a DDR1-activating antibody that specifically binds DDR1 has not been addressed by the as-filed specification. As the result, given the unpredictability of the art and the lack of working example in the instant specification, particularly when taken with the lack of guidance in the specification, it would have required undue experimentation to practice the instant methods to identify an enormous number of methods as broadly or generically claimed,

with a resultant identification of a method of maturation of an iDC or an immature macrophage as broadly claimed.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 57 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language.

Claim 57 has been amended to recite, "the DDR1-activating antibody upregulates chemokines or cytokines". The metes and bounds of this phrase are indefinite because "the DDR1-activating antibody upregulates chemokines or cytokines" can encompass multiple meanings from upregulation of mRNA for any chemokines or cytokines, upregulation of protein level of chemokines or cytokines, production/secretion of chemokines or cytokines by the iDC expressing DDR1, production/secretion of chemokines or cytokines in neighboring cells. As such, the metes and bounds of the claims cannot be determined.

Conclusion

Claims 11-13, 18-25 and 55-60 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Maria Leavitt/

Maria Leavitt
Primary Examiner, Art Unit 1633